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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,412	CERTA ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/12/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/26/02, 8/26/02*, 10/02/03, 1/21/04, 7/30/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-6, in the reply filed on 9/22/2004 is acknowledged.

Claims 7 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 9/22/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for inhibiting human aldolase gene expression and decreasing aldolase enzyme activity in cells *in vitro* after transfection with sense and antisense viral particles, does not reasonably provide enablement for inhibition of expression of any target gene in cells or tissues, in vivo, by administration of viral particles expressing a sense RNA strand and an antisense RNA strand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to a process for inhibiting expression of any target gene from any cell or tissue by administration of viral particles expression a sense RNA strand and an antisense RNA strand targeted to any cell or tissue. Further the claims recite the ssRNA strand is cloned into an alphavirus vector and the target gene is eukaryotic, viral or synthetic and the homologous nucleotide sequence is at least 50 bases in length and is specific for a target gene. Additionally, the claims recite the target gene is a developmental gene, an oncogene, a tumor suppressor gene or an enzyme.

The specification as filed discloses inhibition of human aldolase RNA in BHK cells infected, *in vitro*, with sense viral stocks and antisense viral stocks that are homologous to the human aldolase gene (see Example 4). The specification further discloses human aldolase enzyme activity was decreased in BHK cells that were infected, *in vitro*, with sense viral stocks and antisense viral stocks that are homologous to the human aldolase gene (see Example 5). Additionally, the specification discloses HEK293 cell proliferation was not inhibited after infection with sense viral stocks and antisense viral stocks that are homologous to the human aldolase gene *in vitro* (see Example 7).

There is no guidance in the specification as filed that teaches how to target the claimed viral particles expressing sense and antisense RNA to mammalian cells or tissues *in vivo* or inhibit the expression of specific target endogenous genes of mammalian cells or tissues *in vivo*. Although the specification discloses inhibition of human aldolase RNA in BHK cells infected, *in vitro*, with sense viral stocks and antisense viral stocks that are homologous to the human aldolase gene, such a disclosure would not be considered enabling since the state of antisense and RNAi-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 1-25 encompass a process for delivering a broad range of viral particles expressing any sense RNA and any antisense RNA homologous to any target gene via injection into a broad range of cells or tissue, *in vivo*, to inhibit a broad range of specific target genes in cells or tissues. Although the specification discloses inhibition of human aldolase RNA in BHK cells infected, *in vitro*, with sense viral stocks and antisense viral stocks homologous to a human aldolase gene (see Examples 4), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense and RNAi. Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense

effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2). The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS …is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column).

The state of the art for therapeutic *in vivo* applications for RNAi face similar hurdles as antisense as observed by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). Novina et al. (Nature 2004, Vol.430:161-164) agrees that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph).

Paroo et al. (Trends in Biotechnology 2004, Vol.22(8):390-394) summarizes by stating "[d]eveloping siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles.

However, the duplex nature of siRNA introduced an additional layer of complexity. Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for in vivo experiments or therapeutic development. Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

Although RNAi has been seen as the new magic bullet to silence genes, "...magic bullets need magic guns" (stated by William Pardridge as quoted by Adams in The Scientist (2005) Vol.19:Issue1). Adams notes that researchers have struggled to get their therapies to particular targets and as stated by McCaffrey "[t]heir approach involves injecting large amounts of virus [vectors expressing shRNA] into the tail vein of mice, or into an artery leading to the liver. Its efficient but probably isn't going to work for humans" (see page 2 The Scientist (2005) Vol.19:Issue1).

As outlined above, it is well known that there is a high level of unpredictability in the antisense and RNAi art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely delivery of a broad range of viral particles expressing any sense RNA and any antisense RNA homologous to any target gene via injection into a broad range of cells or tissue, *in vivo*, to inhibit a broad range of specific target genes in cells or tissues.

While one skilled in the art may be able to produce viral particles expressing any sense RNA and any antisense RNA homologous to any target gene, the specification as filed does not

teach a process for delivering any viral particles expressing any sense RNA and any antisense RNA, to inhibit expression of any target gene from any cells or tissue.

Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) supports the difficulties of extrapolating from in vitro experiments and states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

In view of the unpredictability in the art of antisense and RNAi-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of any viral particle expressing any sense RNA and any antisense RNA homologous to a target gene, *in vivo,* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a gene in any cell or tissue. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the polynucleotides *in vivo,* delivery of the polynucleotide via vessel injection, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "wherein said cells or tissues **are/is**". There is insufficient antecedent basis for this limitation in the claim because the use of the word "**are**" would mean including cells and tissues. Claim 1 is drawn to a process of inhibiting expression of a target gene in cells "**or**" tissues and it therefore appears the process of inhibiting expression of a target gene is in either cells or tissues and not both.

Claim 3 recites the limitation "the alphavirus". There is insufficient antecedent basis for this limitation in the claim and it is unclear what particular alphavirus vector contains the ssRNA strands.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Fire et al. (U.S. Patent Number 6,506,559).

The instant claims are drawn to a process for inhibiting expression of any target gene from any cell or tissue by administration of viral particles expression a sense RNA strand and an antisense RNA strand targeted to any cell or tissue. Further the claims recite the ssRNA strand is cloned into a viral vector wherein equal amounts of viral particles containing sense and antisense ssRNA. The claims further recite the target gene is eukaryotic, viral or synthetic and the homologous nucleotide sequence is at least 50 bases in length and is specific for a target gene. Additionally, the claims recite the target gene is a developmental gene, an oncogene, a tumor suppressor gene or an enzyme.

Fire et al. teach a process for inhibiting expression of a target gene in cells or tissues (see column 6, lines 32-45) by administration of a RNA wherein the RNA strands comprise homologous nucleotide sequences to a portion of the said target gene (see column 7, lines 53-68). Fire et al. further teach the double stranded structure can be formed by two complementary RNA strands inside the cell (see column 7, lines 42-53). Further, Fire et al. teach the RNA can be introduced into a cell by a viral construct packed into a viral particle (see column 9, lines 49-55). Fire et al. does not disclose cells are infected with equal amounts of viral particles, this would be inherent in order to form an RNA duplex from two complementary strands. Additionally, Fire et al. teach the length of the homologous nucleotide sequence is at least 50 bases in length (see column 8, lines 1-5). Fire et al. further teach the target gene may be eukaryotic, viral or synthetic (see column 8, lines 12-63) and the target gene may be a

developmental gene, an oncogene, a tumor suppressor gene or an enzyme (see column 11, lines 8-37).

Thus, absent evidence to the contrary, Fire et al. anticipates claims 1-2 and 4-6 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (U.S. Patent Number 6,506,559), in view of Johanning et al. (Nucleic Acids Research 1995, Vol.23(9): 1495-1501).

The instant claims are drawn to a process for inhibiting expression of any target gene from any cell or tissue by administration of viral particles expressing a sense RNA strand and an antisense RNA strand targeted to any cell or tissue. Further the claims recite the ssRNA strand is cloned into the vector of an alphavirus.

Fire et al. teach a process for inhibiting expression of a target gene in cells or tissues (see column 6, lines 32-45) by administration of a RNA wherein the RNA strands comprise homologous nucleotide sequences to a portion of the said target gene (see column 7, lines 53-68). Fire et al. further teach the double stranded structure can be formed by two complementary

RNA strands inside the cell (see column 7, lines 42-53). Further, Fire et al. teach the RNA can be introduced into a cell by a viral construct packed into a viral particle (see column 9, lines 49-55). Fire et al. does not teach the viral construct consists of an alphavirus.

Johanning et al. teach an alphavirus vector that is capable of expressing a single stranded RNA transcript in cells (see page 1498, column 2).

It would have been obvious to one of ordinary skill in the art to substitute the alphavirus vector construct, as taught by Johanning et al. for the generic viral vector, as taught by Fire et al.

One would have been motivated to incorporate the use of alphavirus vectors, as taught by Johanning et al. into the process for inhibiting expression of any target gene from any cell or tissue by administration of viral particles expressing a sense RNA strand and an antisense RNA strand targeted to any cell or tissue because alphavirus vectors have a higher-level of expression than other virus-based vector systems and alphavirus vectors have a broad host range, as expressly taught by Johanning et al. (see page 1500, column 1).

Finally, one would have had a reasonable expectation of success at using Johanning's alphavirus vectors for infecting cells with viral particles containing RNA, as taught by Fire et al., because Johanning et al. expressly teach expression of single stranded RNA transcripts in cells using alphavirus vectors (see page 1500, column 1 and Figures 4-5) and further one would have expected the same level of expression of a RNA transcript as with a ssRNA nucleotide sequence because expression of RNA from a alphavirus vector does not depend on the type of RNA cloned into the alphavirus vector, but depends on the alphavirus vectors introduction into the cell.

Thus in absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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